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(54) Title: **PROCESS FOR PREPARING OF PACLITAXEL**

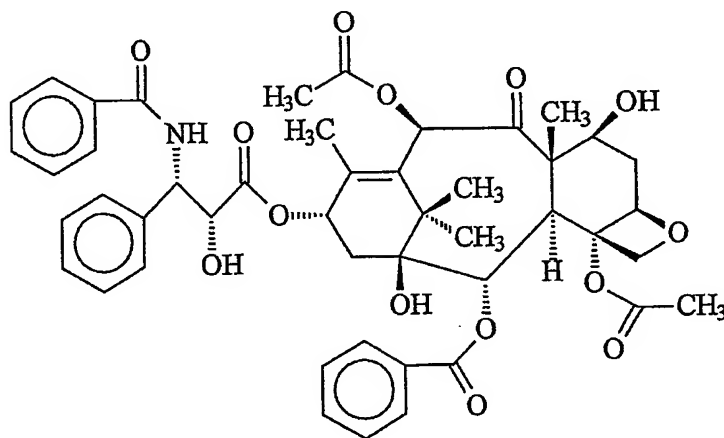
(57) Abstract: A process for making paclitaxel comprises: (a) acetylating 10-deacetyl baccatin-III at the C-10 position in the presence of a tertiary amine base to give baccatin-III; (b) protecting baccatin-III at the C-7 position by reacting baccatin-III with a protecting group; (c) converting the product of step (b) to paclitaxel. Preferably, the protecting group at the C-7 position is 2,2,2-trichloroethylchloroformate.

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PROCESS FOR PREPARING OF PACLITAXEL

The present invention relates to a process for preparing the chemotherapeutic agent paclitaxel.

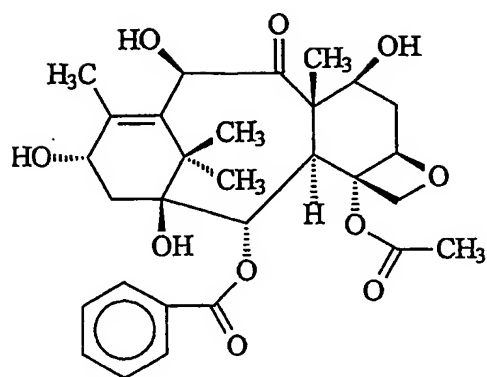
Paclitaxel is a known antineoplastic compound which, if desired, can be isolated from the bark of *Taxus brevifolia* (Western Yew). Its chemical name is 5 β ,20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. The chemical structure is shown below.



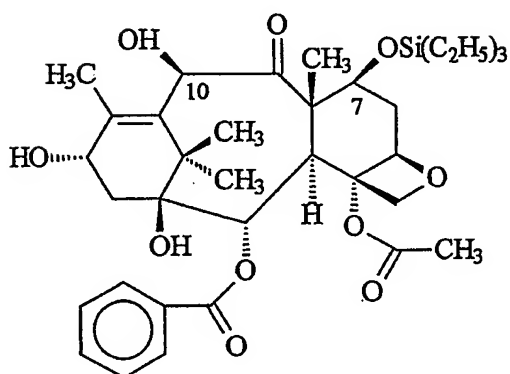
PACLITAXEL

Synthetic and semi-synthetic methods of producing the compound are, however, known. One such method is described in US 5229526 and continuation-in-part US 5274124 to Holton. As with many syntheses, these patents describe a process for obtaining paclitaxel from the compound 10-deacetyl baccatin. The initial steps used are those according to Green *et al* (J. Am. Chem. Soc., 1988, 110, 5917-5919) in which 10-deacetyl baccatin is first silylated and then acetylated according to the following scheme:

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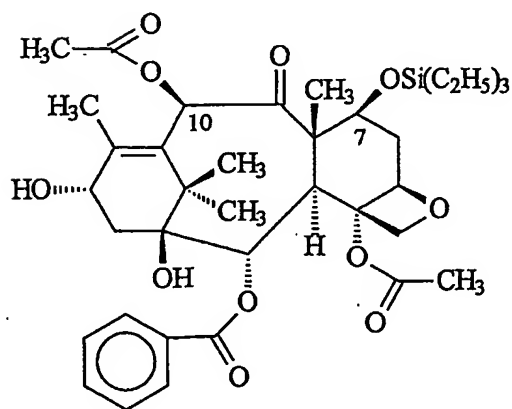


10-deacetyl baccatin III

 $(\text{C}_2\text{H}_5)_3\text{SiCl}$ 

7-triethylsilyl-10-deacetyl baccatin III

acetylation



7-O-triethylsilyl baccatin III

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The yield of the silylated product is reported (in the above patents) to be 84-86% after purification, and the yield of the acetylated product is reported to be 86%. The acetylated product is then converted to paclitaxel via a stereospecific coupling reaction with an appropriate β -lactam followed by deprotection.

Whilst the above-mentioned process is in some respects satisfactory, we have now devised an improved process wherein the yield of intermediate compounds is much greater such that purification of the intermediates is not required.

According to the present invention, there is provided a process for preparing paclitaxel, which process comprises the steps of

- a) acetylating 10-deacetyl baccatin III (I) at the C-10 position in the presence of a tertiary amine base to give baccatin -III (II);
- b) protecting baccatin-III (II) at the C-7 position by reacting baccatin-III with a protecting group;
- c) converting the product of step (b) to paclitaxel.

According to a highly preferred aspect of the invention, in step (b) we prefer to use 2,2,2-trichloroethylchloroformate (Troc) as the protecting group.

Thus, contrary to previous methods, the process of the invention proceeds first by acetylation of 10-deacetyl baccatin III at the C-10 position followed by protection at the C-7 position. We have found that, surprisingly, by carrying out the process in the above manner much greater chemoselectivity is achieved. The result of this is that both baccatin III and the C-7 protected baccatin III derivative are obtained in much greater yield than the intermediates obtained in previous processes. With our process, we have found that the yield of baccatin III is basically quantitative - that is 100% yield, or very close to 100% yield. The C-7 protected baccatin III derivative is also obtained in quantitative, or virtually quantitative yields (that is, 100% yield). For example, when using Troc as the protecting group, we obtain a yield of 7-Troc-baccatin III of from 97 and 100%, depending upon the exact conditions. By contrast, we have found that by employing C-7 protection first using triethylsilyl chloride (TES-Cl) followed by acetylation at the C-10 position (as in the above US patents), the intermediate 7-triethylsilyl-10-deacetyl baccatin III is obtained with 74% yield, and the intermediate 7-triethylsilyl baccatin III is obtained with 78.5% yield. Conversely, the high yields of intermediates obtained by our process means that no additional purification steps, as are conventionally needed, are required although they can of course be employed if desired. In

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conventional methods, purification of the intermediates leads to an overall loss in yields, so by dispensing with this requirement the present process is more economical and efficient.

We have found that the use of a tertiary amine base in step (a) of the process surprisingly speeds up the reaction time of this step to about 1 hour or less and provides a very pure product in virtually quantitative yield. Holton *et al* (Tetrahedron letters 39 (1998) 2883-2886) have reported on the selective protection of the C(7) and C(10) hydroxyl groups in 10-deacetyl baccatin III. For production of baccatin III, the maximum reported yield is 95% (using CeCl_3 and acetic anhydride) which is less than that achieved in the present invention. Furthermore, addition of base is reported by Holton *et al* to induce the formation of 7-acetyl-10-DAB and 7-acetyl baccatin III side products. In contrast, we have found that the use of a tertiary amine base can, in fact, surprisingly give excellent results in terms of reaction time, yield and product purity. Indeed, we have found that repetition of the pertinent Examples from Holton *et al* gives high impurity levels, thus necessitating further purifications. In the present process, any suitable tertiary amine base can be used, for example any member of the trialkylamines (including isomers thereof), for example trialkylamines where each alkyl group is, independently, C_1 to C_{10} . Particularly good results have been achieved using triethylamine, so we prefer to use this compound, although similar compounds can be used. The completion of the reaction within 1 hour or less contributes to an efficient and economical process, and provides considerable advantage for a commercial scale operation.

The acetylation in step (a) can be accomplished using any suitable method. For example, it can be done using acetic anhydride or acetyl chloride. Acetic anhydride can, for example, be used in the presence of CeCl_3 or ZnCl_2 or YbCl_3 employing an organic solvent system, such as tetrahydrofuran (THF).

Any suitable protecting group can be used in step (b), although we prefer to use 2,2,2-trichloroethylchloroformate (Troc). We have found that Troc protection can be employed advantageously in the present process because only mild conditions are required for deprotection. Harsh or strongly acidic conditions, which may affect other parts of the taxane molecule, are therefore avoided. In previous processes, the protecting groups used have required strongly acidic conditions for deprotection, and this results in a crude product with more impurities. In these circumstances, the product is difficult to purify and thus obtained in low yield. Use of Troc in particular avoids these difficulties and thus contributes to higher

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overall yields of product. Other suitable protecting groups include carbobenzyloxycarbonyl, or t-butoxycarbonyl or 9-fluorenylmethoxycarbonyl.

Use of Troc gives the intermediate 7-Troc-baccatin-III (compound III). Advantageously, a catalyst is used to perform step (b). Any suitable catalyst may be used, although we prefer to use a 4-dimethylaminopyridine (DMAP). Other suitable tertiary amines such as triethyl amine, di-isopropyl ethyl amine, N,N-dimethyl aniline can be employed if desired. The use of a catalyst during step (b) helps ensure virtually quantitative yields of product with respect to baccatin-III.

In a highly preferred aspect of the invention, step (b) is performed at less than room temperature (that is, less than about 25°C), preferably at less than 0°C. It is particularly preferred to use a low temperature of, for example, from -5°C to -15°C, suitably from -5°C to -10°C. We have found that the use of a low temperature during this step gives a fewer impurities than when the reaction is done at room temperature, and also reduces the reaction time. Low temperature conditions are particularly suitable when employing Troc as the protecting group.

It is also preferred during step (b) to add the protecting group in two or more lots during the reaction. This helps improve both the yield and purity of the product and, importantly, also reduces the reaction time for this step. Typically, the reaction time is reduced to about 1 hour for addition of two separate lots of protecting group. Addition of the protecting group in two or more lots is particularly preferred when Troc is used, as this gives very good results. For example, addition of Troc in two lots to baccatin III so as to give 7-Troc-baccatin III, using DMAP as catalyst and a temperature of from -5°C to -15°C, gives a quantitative yield of 7-Troc-baccatin III (that is, 100% yield), negligible impurities and a reaction time of 1 hour. Similar results are obtained using suitable catalysts other than DMAP.

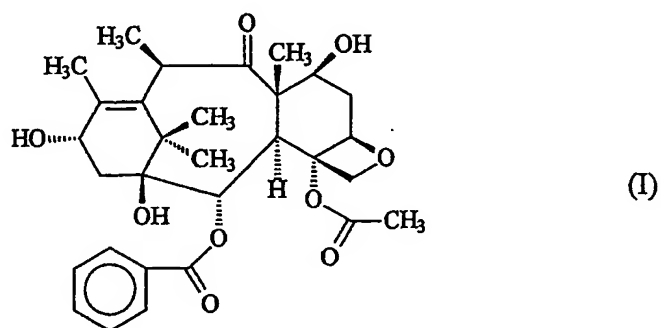
The starting material, 10-deacetyl baccatin III can be obtained according to known procedures. For example, it can, if desired, be obtained from the needles of *Taxus baccata*.

Step (c) involves converting the product of step (b), which is preferably 7-Troc-baccatin III, to paclitaxel, and this can be achieved by any suitable method. One such method is that described in US 5229526 and US 5274124. Typically, step (c) involves coupling the product of step (b) with a suitable compound so as to give a β amido ester side chain at the C-13 position, followed by deprotection at the C-7 position. We prefer to use a suitable β -

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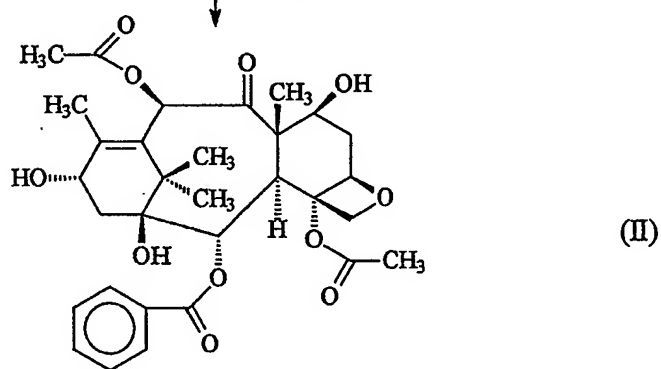
lactam such as, for example, N-benzoyl-3-triethylsilyloxy-4-phenyl azetidin-2-one in the coupling reaction.

A preferred process scheme is as follows:



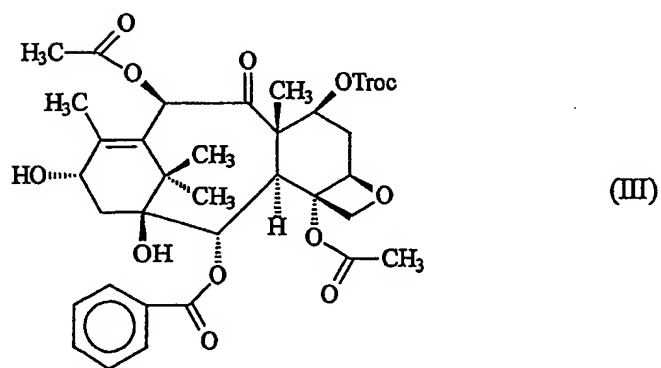
10-deacetyl baccatin III

acetylation



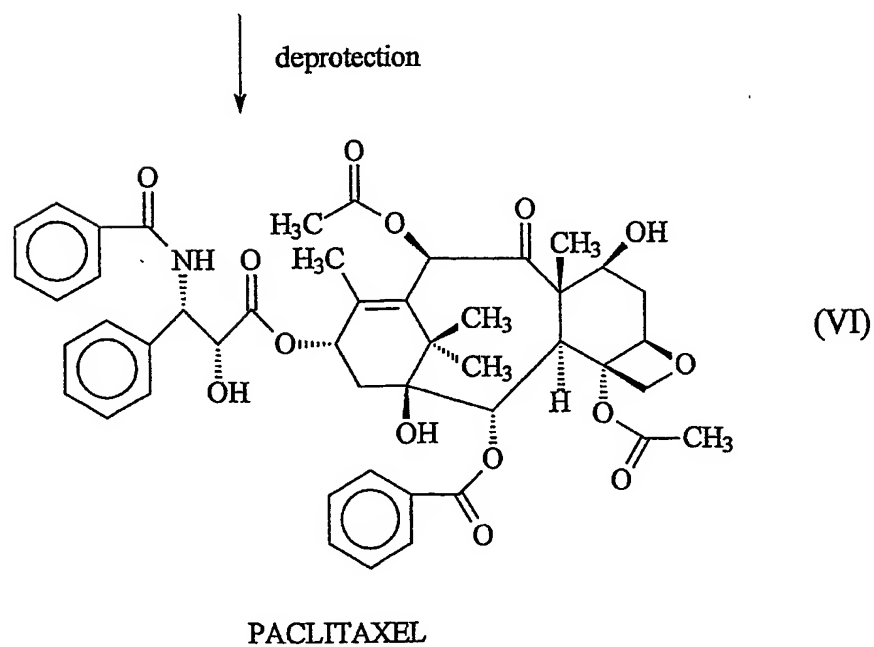
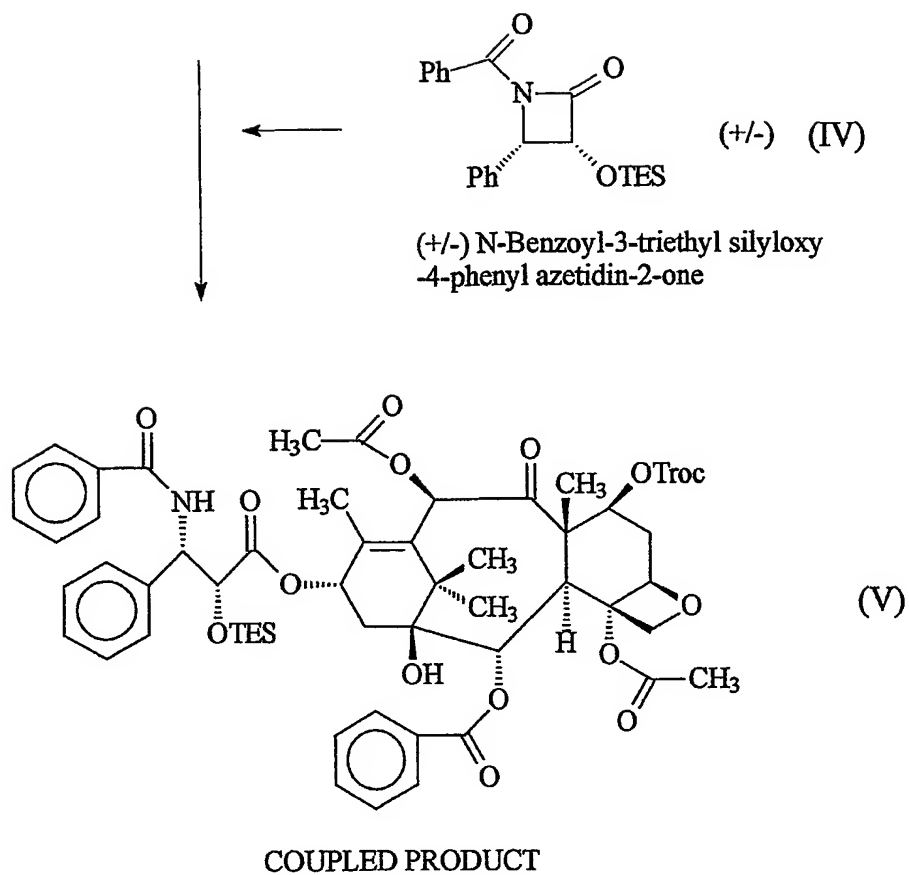
baccatin-III

7-protection with 2,2,2-trichloroethylchloroformate



7-Troc-Baccatin III

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The coupling reaction in step (c) is preferably carried out using 7-Troc-baccatin-III and a racemic mixture of N-benzoyl-3-triethylsilyloxy-4-phenyl azetidine-2-one in the presence of n-butyl lithium. This is an efficient reaction and gives good stereoselectivity. However, other methods of coupling a suitable β -amido ester side chain to the C-7 and C-10 protected baccatin-III intermediate, as will be clear to those skilled in the art, can be used if desired.

Normally, a deprotection step is required following the coupling reaction. Any suitable method of deprotection may be used, although we prefer to avoid using harsh or strongly acidic conditions. Where 7-Troc deprotection is required, the deprotection can, for example, be carried out using zinc and acetic acid. It will be noted in the above illustrated scheme that deprotection occurs at both the C-7 position and in the side chain bearing the triethylsilyl (TES) group.

Paclitaxel made according to the process of the invention can be incorporated into pharmaceutical dosage forms including, but not limited to, capsules, tablets, infusion solutions/suspensions and injection concentrates. As will be clear to those skilled in the art, the above forms may be formulated using appropriate pharmaceutical excipients.

The following Examples illustrate the invention:

Example 1

- (i) To a stirred solution of 100 gm of 10-deacetyl-baccatin-III (I) in 3.8 lts. THF (tetrahydrofuran) under a nitrogen atmosphere, 25 gms CeCl_3 was added followed by addition of 25 mol. eq. of triethylamine. Acetic anhydride (425 ml, 10 mol. eq.) was added at cold to ambient temperature and the reaction mixture was left overnight at cold to ambient temperature under stirring. The reaction was monitored by TLC, eluent heptane/ethyl acetate \neq 1/1. The solution was diluted with water, extracted with ethyl acetate, washed with sodium bicarbonate and brine. It was then dried over sodium sulphate and passed through a short plug of silica gel and the eluant evaporated under reduced pressure to afford 107 gms of baccatin-III (II), melting point 243-245°C.
- (ii) A solution of 200 gms of (II), 100 ml of pyridine and 5.6 gms of dimethylamino pyridine in 4 litres of MDC was stirred at room temperature under nitrogen atmosphere. To the mixture 100 ml (20 eq.) of 2,2,2-trichloroethylchloroformate was added. After 45 minutes an additional 60 ml of 2,2,2-trichloroethylchloroformate was

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added and stirring was continued for another 10 minutes. The reaction was monitored by TLC (CH_2Cl_2 /methanol 9:1). The reaction mixture was diluted with 3.0 litres of MDC and washed with 3.0 litres of aqueous 0.5 N potassium bisulfate, water, saturated NaHCO_3 and brine. The organic layer was dried over sodium sulphate and evaporated to dryness under reduced pressure. The resulting white residue was sonicated in diethyl ether and filtered. Recrystallisation in methanol afforded 260 gms of 7-Troc-baccatin-III (III).

- (iii) 10 gm of (III) was dissolved in 100 ml anhydrous THF under nitrogen atmosphere. n-butyl lithium in hexane 2.5 M, (10.7 ml) was added at -40°C . The reaction mass was stirred at -40°C for 30 minutes. A solution of 27.4 gm of (IV) in 100 ml anhydrous THF was added, between -30°C to -50°C . The temperature of mixture was allowed to rise to 0°C naturally and it was stirred for 1 hour at 0°C . 100 ml of 10% acetic acid/THF was added. The mixture was diluted with 1.0 litre of ethyl acetate and 1.0 litre of saturated NaHCO_3 solution was added. The organic layer was separated and evaporated under reduced pressure. The residue was purified by column chromatography on silica 60, eluent 99:1 CH_2Cl_2 /methanol to get coupled product (V).
- (iv) 30 gm of (V) was dissolved in 80 ml acetic acid, then 20 ml THF, 20 ml water and 15 gm zinc powder was added and reacted at $30-60^\circ\text{C}$. The reaction was monitored by 1:1 acetone/hexane. After completion of the reaction, solid substances were filtered off. The reaction was diluted with 200 ml of ethyl acetate and 200 ml of saturated NaHCO_3 solution were added to the filtrate. The organic phase was separated out and washed with NaHCO_3 , water and brine. The solution was dried over Na_2SO_4 , and evaporated under reduced pressure to dry residue. After column purification, pure paclitaxel (VI) was obtained.

Example 2

Conversion of 10-DAB (10-deacetyl baccatin III) to BAC-III (baccatin-III) using cerium chloride with base

To a stirred solution of 100 mg of 10-deacetyl baccatin-III in 3.8 ml THF (tetrahydrofuran) under a nitrogen atmosphere, 25 mg CeCl_3 was added followed by addition of 25 mol. eq. of triethyl amine. Acetic anhydride (425 microlitre, 10 mol. eq.) was added at cold to ambient temperature and the reaction mixture was stirred for one hour at ambient temperature. The reaction was monitored by TLC, eluent heptane/ethyl acetate; 1:1. The solution was diluted

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with water, extracted with ethyl acetate, and washed with sodium bicarbonate and brine. It was then dried over sodium sulphate and evaporated under reduced pressure to afford the title product. Further purification was done by column chromatography (silica 60-120#, dichloromethane/methanol, 99 : 1) to yield 107 mg baccatin-III (purity: 98%).

Example 3

Conversion of 10-DAB to BAC-III using anhydrous zinc chloride with base

To a stirred solution of 100 mg of 10-deacetyl baccatin-III in 3.8 ml of THF under a nitrogen atmosphere, 88 mg anhydrous zinc chloride (3.5 mol. eq.) was added followed by addition of 88 microlitre of triethylamine. Acetic anhydride (88 microlitre, 5 mol.eq.) was added at ambient temperature and the reaction mixture was stirred at ambient temperature under stirring for one hour. The reaction was monitored by TLC, eluent heptane/ethyl acetate, 1:1. The solution was diluted with water, extracted with ethyl acetate, washed with sodium bicarbonate and brine. It was then dried over sodium sulphate and evaporated under reduced pressure to afford the title product. Further purification to remove trace impurities was done by column chromatography (silica gel 60-120#, dichloromethane/methanol, 99:1) to yield 107 mg of baccatin-III (purity: 99%).

Example 4

Conversion of Baccatin-III to 7-Troc baccatin-III using Troc-Cl in two lots at low temperature

A solution of 200 mg of baccatin-III, 100 microlitre of pyridine and 5.6 mg of dimethylaminopyridine in 4 ml dichloromethane was stirred at -15 C under nitrogen atmosphere. To the mixture 100 microlitre (2.22 mol. eq.) of 2,2,2-trichloroethylchloroformate was added. After 45 min. an additional 60 microlitre (1.28 mol. eq.) of 2,2,2-trichloroethylchloroformate was added and stirring was continued for another 10 min. The reaction mass was stirred for 1-1.5 hrs. at -5 to -15 C. The reaction was monitored by TLC (dichloromethane/methanol, 9:1). The reaction mixture was diluted with 30 ml of dichloromethane and washed with 30 ml of aq. 0.5 N potassium bisulfate, water, saturated NaHCO₃ and brine. The organic layer was dried over sodium sulphate and evaporated to dryness under reduced pressure. The resulting white solid residue was sonicated in diethyl ether and filtered. Recrystallisation in methanol afforded 259 mg of 7-Troc-baccatin-III (purity: 99%).

Example 5 (comparative)Conversion of 10-DAB to BAC-III using cerium chloride without base

To a stirred solution of 100 mg of 10-deacetyl baccatin-III in 3.8 ml THF under a nitrogen atmosphere, 25 mg CeCl_3 was added. Acetic anhydride (425 microlitre, 10 mol. eq.) was added at cold to ambient temperature under and the reaction mixture was stirred for one hour at ambient temperature. The reaction was monitored by TLC, eluent heptane/ethyl acetate; 1:1. Stirring was continued for 3 hours during which monitoring by TLC was done hourly. When an increase in impurity formation was seen in spite of the reaction remaining incomplete, the reaction was stopped and the solution was diluted with water, extracted with ethyl acetate, washed with sodium bicarbonate and brine. It was then dried over sodium sulphate and evaporated under reduced pressure to afford the crude product. Further purification was done by column chromatography. (Silica 60-120#, Dichloromethane/methanol, 99 : 1) to yield 52 mg baccatin-III (purity: 95%). It can be seen that both the yield and purity are much reduced in comparison with Example 2.

Example 6Conversion of Baccatin-III to 7-Boc baccatin-III using ditertiary butyl pyrocarbonate (Boc anhydride) in two lots at low temperature

A solution of 200 mg of baccatin-III, 100 microlitre of pyridine and 5.6 mg of dimethylaminopyridine in 4 ml dichloromethane was stirred at -15°C under nitrogen atmosphere. To the mixture 170 microlitre ditertiary butyl pyrocarbonate (Boc anhydride) was added. After 45 min. an additional 60 microlitre ditertiary butyl pyrocarbonate was added and stirring was continued for another 2 hrs. The reaction was monitored by TLC (dichloromethane/methanol, 9:1). The reaction mixture was diluted with 30 ml of dichloromethane and washed with 30 ml of aq. 0.5 N potassium bisulfate, water, saturated NaHCO_3 and brine. The organic layer was dried over sodium sulphate and evaporated to dryness under reduced pressure. The resulting white solid residue was sonicated in diethyl ether and filtered. Recrystallisation from ethanol afforded 160 mg of 7-boc-baccatin-III (purity: 90%).

Example 7Conversion of Baccatin-III to 7-Troc baccatin-III using Troc-Cl in two lots at room temperature

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A solution of 200 mg of baccatin-III, 100 microlitre of pyridine and 5.6 mg of dimethylaminopyridine in 4 ml dichloromethane was stirred at 25°C under nitrogen atmosphere. To the mixture 100 microlitre (2.22 eq.) of 2,2,2-trichloroethylchloroformate was added. After 45 min. an additional 60 microlitre (1.28 eq.) of 2,2,2-trichloroethylchloroformate was added and the reaction mass was stirred for 1-1.5 hrs. at 25-30°C. The reaction was monitored by TLC (dichloromethane/methanol, 9:1). The reaction mixture was diluted with 30 ml of dichloromethane and washed with 30 ml of aq. 0.5 N potassium bisulfate, water, saturated NaHCO₃ and brine. The organic layer was dried over sodium sulphate and evaporated to dryness under reduced pressure. The resulting white solid residue was sonicated in diethyl ether and filtered. Recrystallisation in methanol afforded 244 mg of 7-Troc-baccatin-III, purity 82%.

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CLAIMS:

1. A process for making paclitaxel, which process comprises (a) acetylating 10-deacetyl baccatin-III at the C-10 position in the presence of a tertiary amine base to give baccatin-III; (b) protecting baccatin-III at the C-7 position by reacting baccatin-III with a protecting group; (c) converting the product of step (b) to paclitaxel.
2. A process according to claim 1 wherein the protecting group in step (b) is 2,2,2-trichloroethylchloroformate.
3. A process according to claim 1 or 2 wherein the tertiary amine base is triethylamine.
4. A process according to any one of claims 1, 2 or 3 wherein step (b) is done at less than 0°C, suitably from -5°C to -15°C or from -10°C to -15°C.
5. A process according to any preceding claim wherein in step (b) the protecting group is added in two or more separate lots to the reaction mixture.
6. A process according to claim 5 wherein the protecting group is 2,2,2-trichloroethylchloroformate.
7. A process according to any preceding claim wherein step (b) is effected using a tertiary amine catalyst, preferably 4-dimethylaminopyridine.
8. A process according to any preceding of claim wherein step (c) is effected by coupling the product of step (b) with N-benzoyl-3-triethylsilyoxy-4-phenyl azetidine-2-one, which compound is preferably used as the racemate, followed by deprotection.
9. A process according to claim 8 wherein said coupling is effected in the presence of n-butyl lithium.
10. A process according to any preceding claim wherein step (c) includes deprotection using zinc and a weak acid such as acetic acid.

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11. A process according to any preceding claim wherein the acetylation step (a) is effected using acetic anhydride, preferably in the presence of CeCl_3 .
12. A process according to any preceding claim wherein triethylamine is used in step (a); and 2,2,2-trichloroethylchloroformate is used in step (b) and is added in two or more lots, with a reaction temperature for step (b) of from -5°C to -15°C .
13. A process according to claim 12 wherein step (b) is effected using a tertiary amine catalyst such as 4-dimethylaminopyridine.
14. 7-[2,2,2-trichloroethylchloroformate]-baccatin-III.
15. Use of the compound of claim 14 to make paclitaxel.
16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and paclitaxel made according to any one of claims 1 to 13.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB 03/03041

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 17656 A (ARMAND-FRAPPIER) 30 April 1998 (1998-04-30) example 2	1
X	page 1; claims; example 2 ---	14-16
A	WO 99 45001 A (BRISTOL-MYERS) 10 September 1999 (1999-09-10) claim 27; figures SCH.2,3; examples	1
X	page 1; claims; examples --- -/--	8-10, 14-16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

25 September 2003

Date of mailing of the international search report

06/10/2003

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KOICHIRO MORIHIRA: "ENANTIOSELECTIVE TOTAL SYNTHESIS OF TAXOL" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 120, no. 49, 1998, pages 12980-1, XP000788257 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 page 12981; figure SCH.1	1
X		8,10
A	F. GUERITTE-VOGELEIN: "CHEMICAL STUDIES OF 10-DEACETYL BACCATIN III." TETRAHEDRON., vol. 42, no. 16, 1986, page 4451-60 XP002025601 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM., NL ISSN: 0040-4020 page 4451 -page 4454; examples	1-3,14, 15
A	R.A. HOLTON: "SELECTIVE PROTECTION OF THE C(7) AND C(10) HYDROXYL GROUP IN 10-DEACETYL BACCATIN III" TETRAHEDRON LETTERS., vol. 39, no. 19, 1998, pages 2883-6, XP004115707 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM., NL ISSN: 0040-4039 page 2883 -page 2885; table 3	1-3
X		14

INTERNATIONAL SEARCH REPORT

information on patent family members

International application No

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9817656	A	30-04-1998	CA 2188714 A1	24-04-1998
			CA 2197369 A1	12-08-1998
			AU 4768797 A	15-05-1998
			WO 9817656 A1	30-04-1998
			US 6410756 B1	25-06-2002
			US 2002045771 A1	18-04-2002
WO 9945001	A	10-09-1999	AU 759988 B2	01-05-2003
			AU 3307899 A	20-09-1999
			CA 2319043 A1	10-09-1999
			EP 1060172 A1	20-12-2000
			HU 0102079 A2	28-12-2001
			JP 2002505326 T	19-02-2002
			WO 9945001 A1	10-09-1999
			US 6020507 A	01-02-2000
			US 6307071 B1	23-10-2001